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Effect of fish oil and coconut fat supplementation on depressive-type behavior and corticosterone levels of prenatally stressed male rats

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ABSTRACT

Prenatal stress (PNS) during critical periods of brain development has been associated with numerous behavioral and/or mood disorders in later life. These outcomes may result from changes in the hypothalamic-pituitary-adrenal (HPA) axis activity, which, in turn, can be modulated by environmental factors, such as nutritional status. In this study, the adult male offspring of dams exposed to restraint stress during the last semester of pregnancy and fed different diets were evaluated for depressive-like behavior in the forced swimming test and for the corticosterone response to the test. Female Wistar rats were allocated to one of three groups: regular diet, diet supplemented with coconut fat or with fish oil, offered during pregnancy and lactation. When pregnancy was confirmed, they were distributed into control or stress groups. Stress consisted of restraint and bright light for 45 min, three times per day, in the last week of pregnancy. The body weight of the adult offspring submitted to PNS was lower than that of controls. In the forced swimming test, time of immobility was reduced and swimming was increased in PNS rats fed fish oil and plasma corticosterone levels immediately after the forced swimming test were lower in PNS rats fed regular diet than their control counterparts; this response was reduced in control rats whose mothers were fed fish oil and coconut fat. The present results indicate that coconut fat and fish oil influenced behavioral and hormonal responses to the forced swimming test in both control and PNS adult male rats.

1. Introduction

Aversive events during pregnancy impair fetal development and produce short- and long-term alterations (Barbazanges et al., 1996; Burlet et al., 2005; Drago et al., 1999; Emack et al., 2008; Lemaire et al., 2006; Morley-Fletcher et al., 2003a; Morley-Fletcher et al., 2003b; Weinstock, 1997). These changes, that have been claimed to result from the exposure to high levels of corticosterone (Catalani et al., 2000; Maccari et al., 2003; Zagron and Weinstock, 2006), include low birth weight, delay in growth and motor development and behavioral impairment in novel situations (Burlet et al., 2005; Drago et al., 1999; Emack

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Abbreviations: PUFAs, polyunsaturated fatty acids; PNS, prenatal stress; CTL, control; HPA, hypothalamic-pituitary-adrenal; FST, forced swimming test; IL-1, interleukin-1

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et al., 2008; Hauser et al., 2006; Patin et al., 2004; Secoli and Teixeira, 1998). Corticosterone secretion can be modulated by nutritional factors, provided either pre- or post-natally. Thus, the 10 day-old offspring of dams fed with fat-rich diets secrete less corticosterone after ether stress (Trottier et al., 1998), whereas adult rats fed with the same type of diet secrete more corticosterone than regular chow fed rats (Tannenbaum et al., 1997).

Polyunsaturated fatty acids (PUFAs) are cell membrane constituents essential for the proper functioning and cell response to various stimuli. They are essential fatty acids, e.g., obtained only from diet, and their precursors are linoleic acid or omega-6 (18:2n-6) and alpha-linolenic acid or omega-3 (18:3n-3) (Spector, 1999; Yehuda, 2003). The main omega-3 PUFA metabolites are the eicosapentaenoic acid (20:5n-3) and docosahexaenoic acid (22:6n-3), while the main metabolite of omega-6 is arachidonic acid (20:4n-6). PUFAs are transferred from the mother to the fetus through the placenta and to the offspring through the milk, in such a way that plasma or cellular levels reflect maternal diet (Amusquivar et al., 2000; Carlson, 2009; Innis, 2008; McNamara and Carlson, 2006; Trottier et al., 1998; van Goor et al., 2008).

Administration of omega-3 during pregnancy, lactation and/or weaning, reduces immobility time in the forced swimming test in the adult offspring, suggesting an anti-depressant effect (Ferraz et al., 2008; Naliwaiko et al., 2004); this same effect is observed when supplementation takes place only in adulthood (Carlezon et al., 2005; Huang et al., 2008; Venna et al., 2009). Furthermore, omega-3 supplemented diets significantly reverse anxiety-like behavior, corticosterone secretion and inflammatory responses induced by central administration of the cytokine IL-1β (Song et al., 2003). Taking into consideration that PNS induces depressive-like behavioral changes and that intake of omega-3 inversely correlates with incidence of depression (Alonso et al., 1991; Hibbeln, 1998; Morley-Fletcher et al., 2003a; Morley-Fletcher et al., 2004), the purpose of the present study was to examine the long-term impact of the interaction between omega-3 treatment during pregnancy/lactation and prenatal stress in regards to depressive-like behavior and corticosterone secretion in the adult male offspring.

2. Results

Body weight (Fig. 1): Analysis of body weight in the first day of life showed a main effect of PNS [$F(1,140)=7.19$; $p=0.008$], but no effect of diet [$F(2,140)=1.22$; $p=0.299$] nor an interaction between factors [$F(2,140)=1.69$; $p=0.189$]. Newman–Keuls test revealed that PNS caused a reduction of body weight in newly-born pups, compared to control pups ($p=0.007$).

As for the body weight of the adult offspring, ANOVA revealed an effect of group [$F(1,53)=10.19$; $p=0.002$], but no effect of diet [$F(2,53)=0.56$; $p=0.572$] nor an interaction between factors [$F(2,53)=2.12$; $p=0.129$]. The *post hoc* test showed that PNS rats weighted less than control (CTL) rats ($p=0.004$).

Forced swimming test (FST – Fig. 2): There was a group effect on immobility time [$F(1,53)=5.08$; $p=0.03$], but no effect of diet [$F(2,53)=0.31$; $p=0.731$] nor an interaction between the factors [$F(2,53)=1.82$; $p=0.172$]. The Newman–Keuls test indicated that PNS rats displayed less immobility time than CTL rats ($p=0.03$).

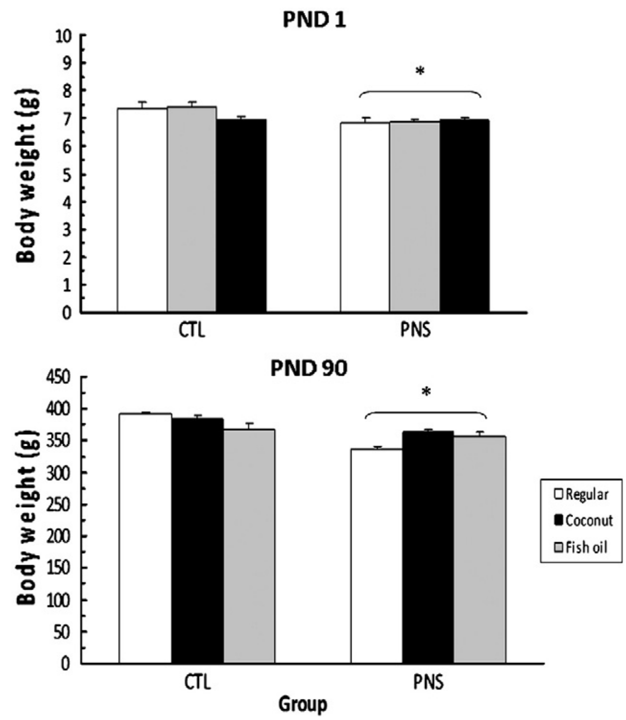

Fig. 1 – Body weight of newly-born (upper panel) and of adult (lower panel) male control (CTL) and prenatal stress (PNS) rats whose mothers were fed regular diet or supplemented with coconut fat or fish oil. Data are presented as mean ± SEM of 9 to 11 animals/group/diet. *–Difference from respective CTL group; $p<0.05$.

Analysis of swimming behavior revealed main effects of group [$F(1,53)=4.36$; $p=0.04$] and diet [$F(2,53)=3.70$, $p=0,03$], but no interaction [$F(2,53)=2.88$; $p=0.06$]. Newman–Keuls test showed that PNS rats spent more time swimming than CTL rats ($p=0.04$) and that fish-fed groups swam longer than regular diet-fed groups ($p=0.02$).

There was a main effect of diet in climbing behavior [$F(2,53)=5.61$; $p=0.006$], but no effect of group [$F(1,53)=0.1$; $p=0.753$] nor an interaction between these factors [$F(2,53)=1.83$; $p=0.17$]. The *post hoc* test indicated that fish oil-fed groups spent less time climbing than regular- and coconut fat diet-fed groups ($p<0.01$).

Open field activity (Fig. 2, insert): There were no effects of group [$F(1,53)=2.11$; $p=0.152$], diet [$F(2,53)=0.86$; $p=0.430$], or interaction between factors [$F(2,53)=3.12$; $p=0.052$] in the locomotor activity measured in the open field.

Adrenals' weight: There were no effects of group [$F(1,53)=1.01$; $p=0.3$], diet [$F(2,53)=0.37$; $p=0.7$] or an interaction between these factors [$F(2,53)=0.32$; $p=0.7$] (Table 2).

Corticosterone plasma levels (Fig. 3): ANCOVA showed an interaction between group and diet [$F(2,52)=4.755$; $p<0.02$] and group and time-point [$F(2,104)=4.749$; $p<0.01$]. The Newman–Keuls test revealed that CTL rats fed regular diet displayed the highest corticosterone levels ($p<0.001$ compared to the other diets and to PNS counterparts). Analysis of the

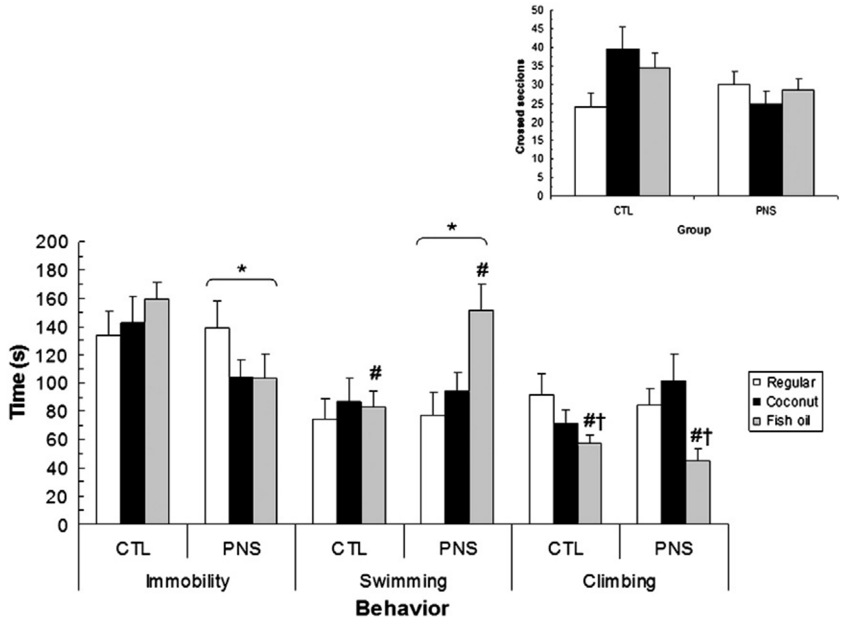

Fig. 2 – Mean ± SEM of the immobility time, swimming and climbing behaviors in the forced swimming test of adult male rats ($n = 9–11$/group). ANOVA, followed by Newman–Keuls test * $p < 0.05$ represents the difference between CLT and PNS groups; # $p < 0.05$ represents the difference between fish oil and regular diet; † $p < 0.05$ represents the difference between fish oil and coconut fat. The insert shows the number of squares crossed (mean ± SEM) in the open field (locomotor activity) obtained immediately after the FST.

group × time-point interaction showed that for CTL rats, hormone levels were equally higher at 5 and 20 min than at 60 min ($p < 0.001$) and for PNS rats, levels at 20 min were higher than at 5 and 60 min ($p < 0.05$).

3. Discussion

The results of the present study showed that PNS in the third week of pregnancy resulted in lower body weight at birth, which remained into adulthood. Low birth weight has been associated with increased susceptibility to stress and depression (Gale and Martyn, 2004). When, however, PNS animals whose mothers were fed with regular diet were tested in the forced swimming test, their behavior was very similar to CTL counterparts. Interestingly, coconut fat and fish oil reduced the immobility time and fish oil increased the swimming time only in PNS. Although the statistical analysis failed to show interactions between group and diet, a close inspection of the values shown in Fig. 2 indicated an anti-depressant effect of both types of fat only in PNS animals. This effect of coconut oil may be explained by its anti-oxidant profile (Marina et al., 2009) and by the fact that it increases the concentration of omega-6 and omega-9 in the cerebral cortex and hippocampus of rats (Naliwaiko et al., 2004), which may confer neuroprotective properties to this oil.

The behaviors displayed in the forced swimming test discriminate between drugs that act at the level of serotonergic and noradrenergic systems, as selective inhibitors of serotonergic reuptake increase swimming behavior and those of noradrenergic reuptake increase climbing behavior (Cryan et al., 2002; Cryan et al., 2005). The fact that fish oil decreased climbing behavior may suggest a reduction of the noradrenergic tone.

There is some controversy in regards to the effects of PNS on depressive-type behavior. Most studies show an increase in immobility time and a positive correlation between this behavior and corticosterone secretion (Alonso et al., 1991; Maccari and Morley-Fletcher, 2007; Morley-Fletcher et al., 2003a). Others, however, do not find any effect of PNS on depressive-type behavior in male rats (Frye and Wawrzycki, 2003; Van den Hove et al., 2005). Recent data may provide an explanation for the discrepant results hereby presented. In the

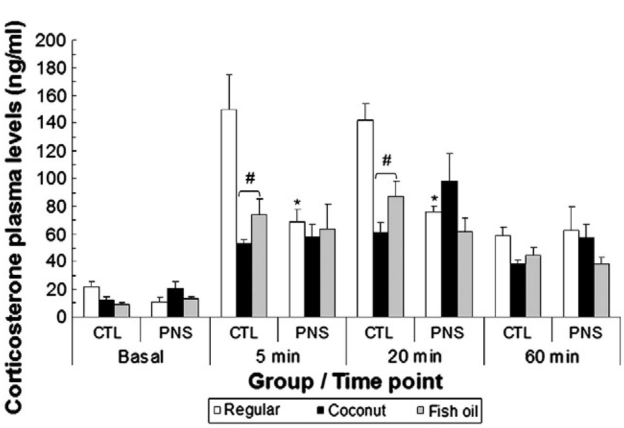

Fig. 3 – Mean ± SEM of baseline corticosterone levels and after the exposure to FST of adult male rats ($n = 9–11$/group/diet). * $p < 0.05$ represents the difference between CTL and PNS; # $p < 0.05$ represents the difference between regular diet × coconut fat and fish oil.

last years, some studies have indicated that animals exposed to early adversity, e.g., prenatal stress, poor maternal care, maternal deprivation, are less affected by stressful situations in adulthood (Champagne et al., 2009), and they perform better under highly stressful conditions, especially in memory tasks that involve aversive stimuli, such as contextual fear conditioning (Bagot et al., 2009; Champagne et al., 2008; Guijarro et al., 2007; Oomen et al., 2010).

Rats submitted to PNS and fed regular diet secreted less corticosterone in response to the test than CTL rats. Moreover, in CTL rats, coconut and fish diets also lowered corticosterone levels compared to regular diet. Although most studies report that PNS leads to augmented corticosterone levels, Van den Hove and co-workers (2005) found a reduction of stress-induced corticosterone levels, and even suggested that PNS could be protective or adaptive. Importantly, in the present study, the neonatal development of the rats was followed-up until weaning, and involved frequent handling of the animals. Some studies show that certain postnatal manipulations, such as handling, adoption, environmental enrichment and diazepam treatment, can reverse or abolish the effects of PNS (Drago et al., 1999; Lemaire et al., 2006; Maccari et al., 1995; Morley-Fletcher et al., 2003b; Secoli and Teixeira, 1998).

Diets containing PUFAs attenuate or block the behavioral and biochemical anxiogenic-inducing effects of IL-1 i.c.v. administration, measured in the elevated plus maze, as well as the elevation of corticosterone (Song et al., 2003). These data suggest that PUFAs reduce the stress response and help to maintain HPA axis integrity. Recent data also show that omega-3 supplementation prevents the expression of depressive-type behavior of rats submitted to the FST (Carlezon et al., 2005; Huang et al., 2008; Venna et al., 2009) and potentiates imipramine effect (Venna et al., 2009). More specifically, Naliwaiko and colleagues (2004) showed that omega-3 supplementation during pregnancy, lactation and adulthood produced anti-depressant effects. Moreover, this beneficial effect can be seen regardless of the period in which omega-3 is offered, preventing the development of depressive-type behavior (Ferraz et al., 2008). This result, however, was not observed in the FST in another study using acute or chronic omega-3 supplementation (Shaldubina et al., 2002). Our results are in agreement with the abovementioned behavioral findings and showed that both coconut fat and fish oil, as well as PNS, reduced corticosterone secretion. In addition, swimming behavior was augmented, whereas climbing was reduced in the groups that received fish oil compared to regular diet. Therefore, the literature data seem contradictory as to the effects of omega-3, but the divergences could be explained by numerous factors, such as the way that omega-3 is supplemented, PUFA's origin, and the amount of other PUFAs in the oil or diet. In a study on the effects of PUFA on epilepsy, alpha-linolenic acid, but not its derivatives docosahexaenoic acid and eicosapentaenoic acid, was shown to be important for the behavioral effects (Porta et al., 2009).

In conclusion, the present data support the idea that PNS caused long-term behavioral and hormonal changes in adulthood and that coconut fat and fish oil exerted anti-depressant effects and reduced corticosterone stress-induced levels in control animals.

4. Experimental procedures

4.1. Subjects and diets

All procedures were carried out in accordance with the guidelines of the National Institute of Health (NIH) and approved by the Ethics Committee in Animal Research of UNIFESP (protocol #: 1689/05).

Two-month old virgin female Wistar rats, weighing an average 281 g, were kept under a 12 h light/12 h dark cycle (lights on at 07:00 AM) in a temperature-controlled room (23 ± 2 °C). Food and water were available ad libitum. The dams were provided one of the three diets: regular diet (n = 20, PNS = 12 and CTL = 8), fish oil-supplemented diet (n = 12, PNS = 7 and CTL = 5) and coconut fat-supplemented diet (n = 10, PNS = 5 and CTL = 5). Animals from both supplemented groups were adapted to the diets for two weeks before the beginning of the study and then were mated with sexually experienced Wistar males. The supplementation was offered throughout pregnancy (21 days) and lactation (21 days). The day of birth was considered postnatal day (PND) 0 and on PND 1, litters were culled to 10 pups (5 males and 5 females). Only the male offspring was used in this study and 2 to 3 male siblings were taken from each litter to avoid litter effect. The final number

Table 1 – Fatty acids composition of regular and diets supplemented with coconut fat or fish oil.

Fatty acids	Regular diet	Coconut fat-supplemented diet	Fish oil-supplemented diet
Saturated			
C6:0 caproic	0.00	<50	0.00
C8:0 caprilic	0.00	448	0.00
C10:0 capric	0.00	426	0.00
C12:0 lauric	0.00	5730	<50
C14:0 miristic	0.00	1825	880
C15:0 pentadecaenoic	0.00	0.00	70
C16:0 palmitic	698	1642	2021
C17:0 margaric	0.00	0.00	57
C18:0 stearic	140	395	349
C20:0 araquidic	<50	<50	<50
C22:0 behenic	<50	<50	<50
Monounsaturated			
C14:1 miristoleic	0.00	0.00	<50
C16:1 palmitoleic	0.00	0.00	992
C17:1 heptadecenoic	0.00	0.00	<50
C18:1 cis-octadecenoic Ω-9	1113	2614	1395
C20:1 eicosaenoic	<50	<50	83
Polyunsaturated			
C18-2 linoleic Ω-6	2510	2150	1811
C18-3 linolenic Ω-3	212	148	251
C20:5 eicosapentaenoic Ω-3	0.00	0.00	1007
C22:6 docosahexaenoic Ω-3	0.00	0.00	884
Total lipid *	6.81	17.14	17.29

Contents are expressed in mg/100 g, * expressed in g/100 g.

of adult males/group/diet were: CTL-regular diet=9, CTL-coconut fat=10, CTL-fish oil=10, PNS-regular diet=9, PNS-coconut fat=11, and PNS-fish oil=10.

The diets were supplemented by adding 11% of fish oil (Sigma®, USA) or coconut fat to regular diet (Nuvilab® rat chow). The fish oil contained approximately 15% of eicosapentaenoic acid and 15% of docosahexaenoic acid, while coconut fat is rich in saturated fatty acid. The concentration of fish oil was based on the studies by Watanabe and colleagues (Watanabe et al., 2010; Watanabe et al., 2009). Antioxidant butilhidroxitoluen was also added (0.02%) and all diets were balanced in protein, differing only in fat content (Table 1). The supplemented diets were prepared twice a month (Borsonelo et al., 2007) and stored in a refrigerator at 4±2 °C.

4.2. *Prenatal stress*

Mating was monitored by taking daily vaginal smears. The presence of sperm in the smear was considered day zero of conception. PNS was carried out between days 14 and 20 of pregnancy as previously reported (Barbazanges et al., 1996; Maccari et al., 1995; Ward and Weisz, 1984). Briefly, pregnant females were individually placed in plastic cylinders of 18 cm in length and 6 cm in diameter and exposed to bright light for 45 min. Animals were daily submitted to three stress sessions starting at 09:00 AM, 12:00 PM and 04:00 PM, whereas CTL pregnant females were left undisturbed in their home cages. Early development of the litters was followed-up until weaning. Two to three pups were used per group to avoid litter effect.

4.3. *Behavioral test*

4.3.1. *Forced swimming test*

Animals were tested at 90 days of age. The test was performed using a modification from the original test described by Porsolt and co-workers (1978) that includes a pre-test (Detke et al., 1997; Lucki, 1997). The rats were individually placed into a container 50 cm high and 30 cm in diameter, containing water up to 30 cm at 25 °C. The animals remained in the water for 15 min (training session) before being removed, dried and returned to their home cage. The second exposure to the FST occurred 24 h later, and rats were allowed to swim for 5 min (test session), during which immobility, swimming and climbing times were recorded. The rat was considered immobile when it floated without struggling and only made the movements necessary to keep its head above the water; swimming was classified as the coordinated movements of upper and lower limbs more than those necessary to maintain the head above the water; climbing was defined as making active movements with forepaws in and out of the water, usually directed against the walls (Detke et al., 1997). The test sessions were carried out between 9:30 AM and 03:00 PM and videotaped for later analysis by ECB, who was blind to the experimental conditions.

4.3.2. *Open field*

Immediately after the FST, each rat was placed in a wood box, measuring 60×60×30 cm, divided in 20×20 cm squares for analysis of locomotor behavior for 5 min (Andrade et al., 2005). The purpose of this test was to determine possible changes in locomotor activity that could interfere with behavior in the FST.

4.4. *Blood sampling and corticosterone assay*

Corticosterone levels of adult rats were determined in four blood samples withdrawn from the tail: basal, immediately (5 min), 20 min and 60 min after the test session. Sampling yielded 100–150 μL of blood. Basal samples were collected two days before the test to avoid possible interference from the stress of sampling on the FST; post-FST samples were collected at the same time as basal samples (10:00 AM). Blood was collected in pre-cooled plastic Eppendorf vials containing a 6% EDTA solution and centrifuged at 2400 rpm for 20 min at 4 °C. Plasma was collected in clean Eppendorf vials and stored at −20 °C.

Corticosterone levels were determined, in duplicate, by a double antibody radioimmunoassay method, specific for rats and mice, using a commercial kit (ICN Biomedicals, Costa Mesa, CA), modified by Thrivikraman and colleagues (1997). The sensitivity of the assay is 3.125 ng/mL, and intra-assay and inter-assay variations are, respectively, 7.1% and 10.3%.

Adrenals were excised, cleaned of surrounding fat and weighed as a pair. Relative adrenal weight was determined by the equation: r=(adrenals' weight/animal's weight)×100.

4.5. *Data analysis*

A two-way ANOVA, with factors group (CTL and PNS) and diet (regular, coconut, fish), was used to analyze the body weight, immobility, swimming, climbing and locomotor activity. Corticosterone plasma levels were analyzed by ANCOVA for repeated measures (time-point: 5 min, 20 min, 60 min), using basal levels as the co-variate. Inter-group effects were detected by the Newman–Keuls *post hoc* test. The level of significance was set at $p \leq 0.05$ for all analyses.

Table 2 – Relative adrenal weights of male adult rats submitted to prenatal stress during the last week of intra-uterine development. Regular or supplemented diets were offered to the dams during pregnancy and lactation. Data are presented as mean±s.d. of 9–11 animals/group/diet.

Control			Prenatal stress		
Regular (9)	Coconut (10)	Fish oil (10)	Regular (9)	Coconut (11)	Fish oil (10)
0.147±0.03	0.148±0.02	0.154±0.03	0.162±0.02	0.150±0.02	0.158±0.03

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